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CASE REPORT

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# Long-term outcomes of destructive seronegative (rheumatoid) arthritis – description of four clinical cases

Elena Nikiphorou<sup>1</sup>, Christopher Sjöwall<sup>2</sup>, Pekka Hannonen<sup>1</sup>, Tuomas Rannio<sup>1</sup> and Tuulikki Sokka<sup>1,3\*</sup>

## Abstract

**Background:** Seronegative rheumatoid arthritis is associated with a milder course of progression compared to seropositive disease. However, long-term follow-up data of the clinical course of seronegative rheumatoid arthritis are sparse. Here we describe four cases with a rare disease entity of aggressive destructive seronegative (rheumatoid) arthritis with 20–35 years of follow-up.

**Case presentation:** The four cases are women with an initial presentation of seronegative rheumatoid arthritis in 1980–1996 and have received disease-modifying anti-rheumatic drugs since the diagnosis. In all cases, the condition has been refractory to treatments and evolved into a severe disease with destructions of the wrists, sub-talar and ankle joints, as well as large joints but not small joints of fingers and toes. All cases are negative with regard to rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antibodies against carbamylated proteins.

**Conclusions:** This report adds to the existing literature, making the reader aware of this sub-type of inflammatory arthritis which despite being seronegative, can have devastating disease consequences. The report highlights the need for further research into this field in order to better understand this disease sub-type, the pathogenesis, disease course and outcomes.

**Keywords:** Rheumatoid arthritis, Seronegative, Erosions, Outcomes

## Background

Classification criteria for rheumatoid arthritis (RA) have evolved over the decades. Positive serology receives special emphasis in the current criteria [1]. In addition to rheumatoid factor (RF) and anti-cyclic citrullinated peptide (aCCP) antibodies, other RA-related antibodies have recently been identified. These include antibodies against carbamylated proteins (aCarP) [2] and malonaldehyde-acetaldehyde [3], albeit none of these are currently included in classification criteria or used in routine clinical practice.

Autoantibodies are believed to have a pathogenetic role in RA [4]. In studies examining predictors,

associating factors, or prevention of RA, seropositive and seronegative groups of patients seem to behave differently [5–7]. In treatment recommendations for RA, seropositivity is recognized as an indicator of severe disease and in these patients, the thresholds for earlier and more intensive/potent disease-modifying treatment are lower [8]. It has become increasingly apparent that our knowledge concerning the pathogenesis, treatment responses and clinical course of seronegative RA, is limited [9, 10].

Up to 20–30 % of patients recruited into RA cohorts and clinical trials are seronegative [11, 12]. An exception is the Finnish Heinola Rheumatism Foundation Hospital early RA cohort from the middle 1970's, which included long-term (25 years) follow-up of seropositive patients only, as experienced rheumatologists were convinced that seropositive disease (positive RF alone at that time) is the only true presentation of

\* Correspondence: tuulikki.sokka-isler@ksshp.fi

<sup>1</sup>Rheumatology/Medicine, Jyväskylä Central Hospital, Keskussairaalantie 19, FI-40620 Jyväskylä, Finland

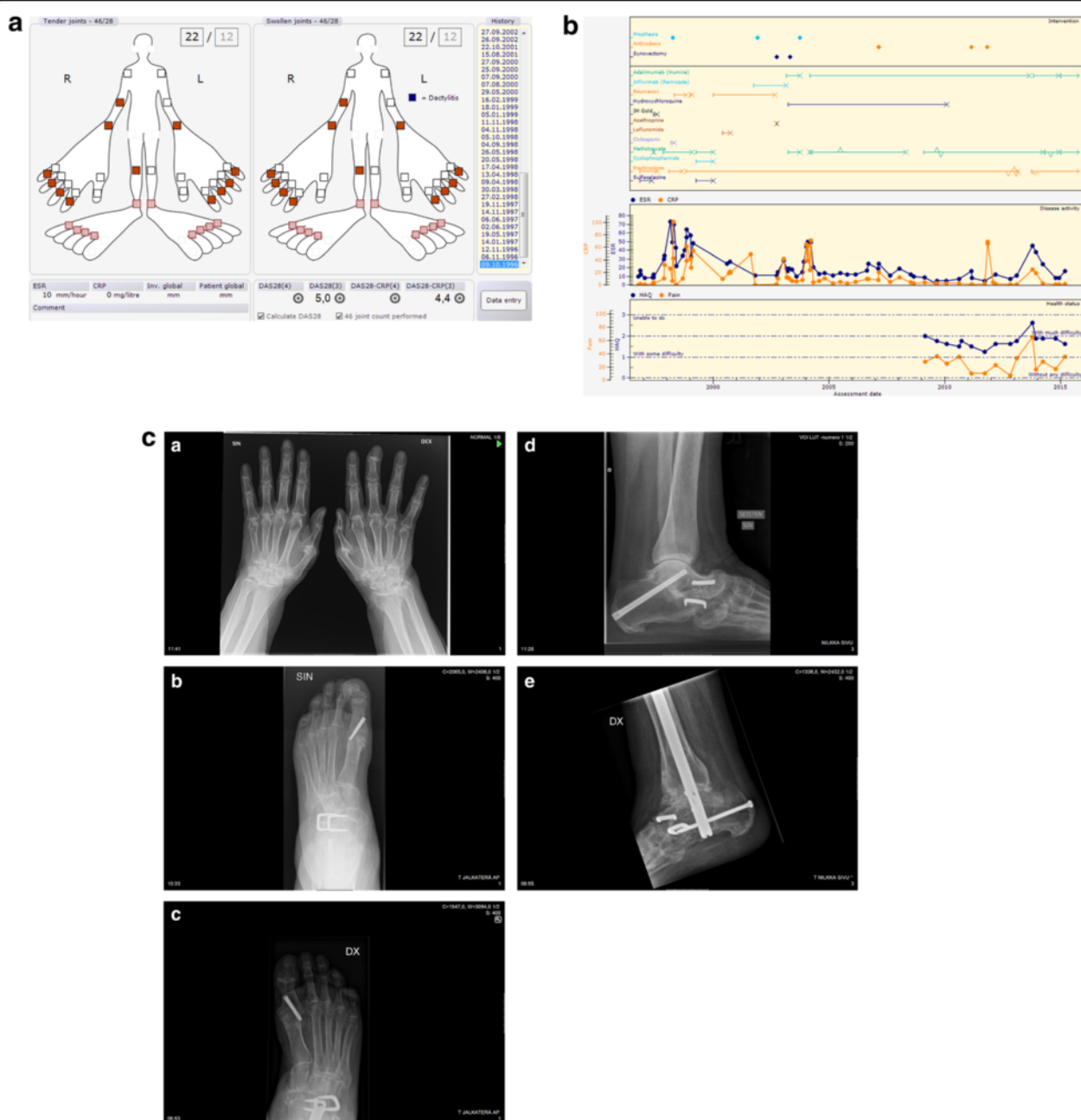
<sup>3</sup>Faculty of Health Sciences, University of Eastern Finland, Jyväskylä Central Hospital, Keskussairaalantie 19, 40620 Jyväskylä, Finland

Full list of author information is available at the end of the article



Observations in our early RA cohorts indicate that long-term radiographic outcomes are different between seropositive and seronegative patients [14]. The natural course of seropositive disease is that of progressive erosions [15], while even in the long-

term (e.g. over 20 years), seronegative patients do not present with marked erosions [16]. However, among >3000 patients included in the Jyväskylä Central Hospital clinical RA database since the 1990's we identified a few consistently RF and aCCP negative individuals with a particular presentation of aggressive, destructive disease. Four cases are presented in detail herein.



**Fig. 1** **a** Initial clinical presentation of Patient 1. **b** Progress of Patient 1. **c** 1-5. Most recent radiographs of Patient 1 (16-19 years from diagnosis)

## Case presentation

### Case 1

Demographics: 68 year old female, diagnosed at the age of 50 in 10.1996. Shopkeeper, work disabled since the diagnosis; former smoker.

Initial presentation: Swelling and tenderness starting in the right knee in 01.1996. Intra-articular glucocorticoid injections administered into the right knee four times, until arthroscopy in 08.1996 with macro- and microscopic finding of synovitis. Joint symptoms gradually evolved resulting in the diagnosis of clinical polyarthritis in 10.1996. See Fig. 1a.

Comorbidities and Joint surgery: See Table 1.

Medications: Current medications, see Table 1. Previous synthetic and biologic disease modifying anti rheumatic drug (DMARD) treatments were (in order of use): sulfasalazine, gold intra muscular (IM), podofyllotoxin (Reumacon), ciclosporin, cyclophosphamide, leflunomide, infliximab, azathioprine, and hydroxychloroquine, see Fig. 1b.

Progress: See Fig. 1b. Most recent values for patient reported outcomes and disease activity: HAQ 1.63, pain 35, fatigue 6, patient global 30, ESR 16, CRP 2, DAS28 3.4 indicating moderate disease activity.

Radiographic features: Radiographs on presentation showed no joint damage. The most recent radiographs of hands, wrists, feet, and ankles, taken 16-19 years after diagnosis, are shown in Fig. 1c. Prominent features include joint space narrowing and subluxation of bones in left wrist and meta carpo phalangeal MCP joints, destruction and operation of subtalar, talonavicular and naviculo-cuneiform joints, as well as right ankle. Typical erosions, seen as in seropositive RA patients are missing.

### Case 2

Demographics: 39 year old female, diagnosed at the age of 16 in 07.1992. Working as a civil engineer. Never smoked.

Initial presentation: The patient sustained a left knee strain while running in 3.1992; symptoms spontaneously resolved within 3 weeks. She was noted to have hyperextension of the left knee in 6.1992 with 7.1992 with synovial fluid aspiration showing 14.000 leucocytes (98 % granulocytes) and a clinical presentation of polyarthritis as shown in Fig. 2a.

Comorbidities and Joint surgery: See Table 2.

Medications. Current medications see Table 2. Previous DMARD treatments included (in order of use): i.m. gold, sulphasalazine, podofyllotoxin (Reumacon), hydroxychloroquine, infliximab, and rituximab see Fig. 2b.

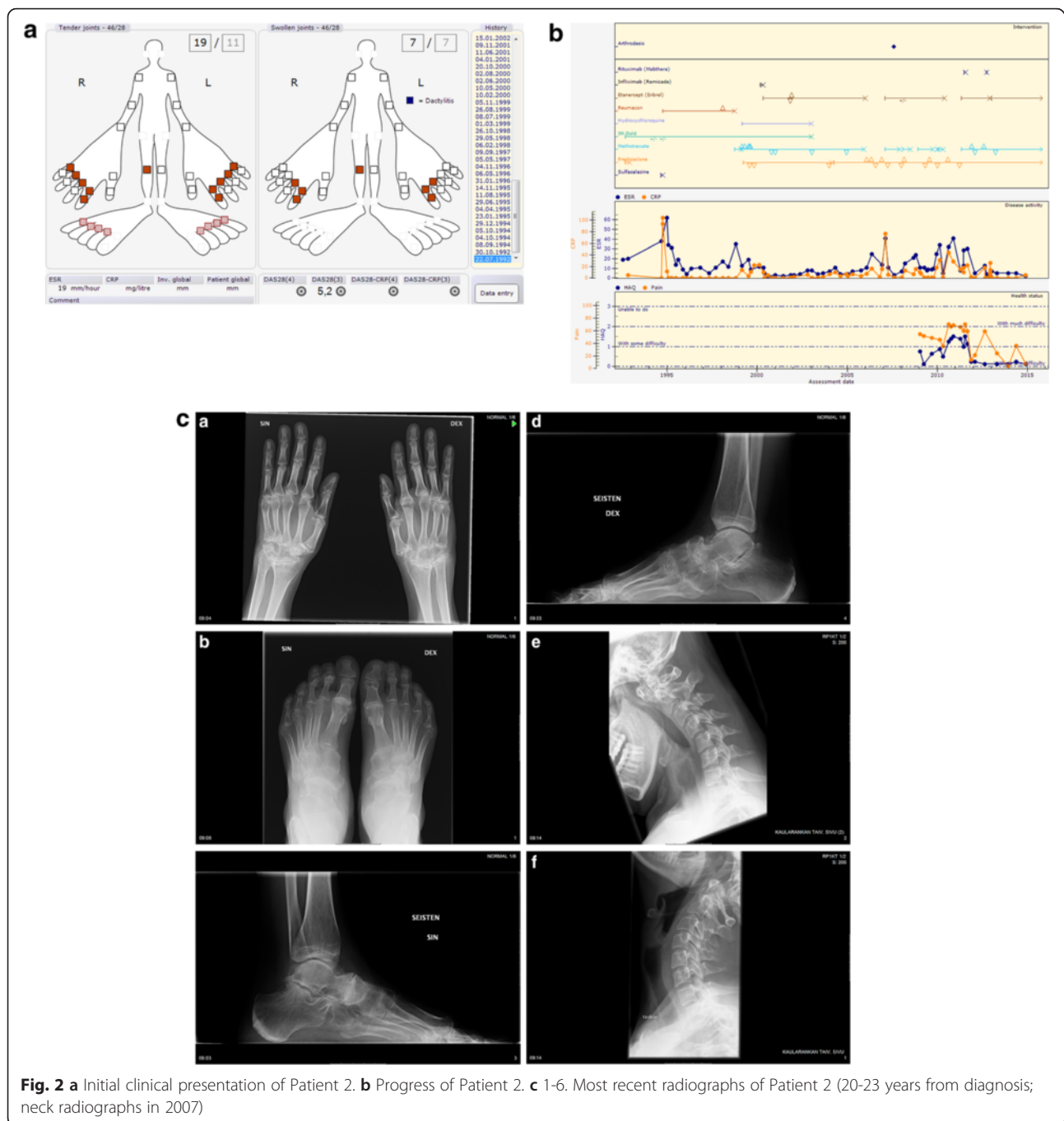
Progress: See Fig. 2b. Most recent values for patient reported outcomes and disease activity: HAQ 0.13,

**Table 1** Medical history of Patient 1

Data extracted	25.08.2015
ID	Case 1
Age, Gender	68, Female
Work status	Pensioner since diagnosis
Diagnosis	Rheumatoid Arthritis
Diagnosis criteria	- Symptoms: 1.1996 - Clinical diagnosis of RA: 10.1996
Highest RF (IgM)	Negative (9) 3.2012
Highest (aCCP)	Negative (4) 8.2009
aCarP	Negative 7.2015
HLA-B27	Positive
Drug (now)	Methotrexate 1.2015 - 7,50 mg Subcutaneous Once a week Adalimumab (Humira) 1.2015 - 40,00 mg Subcutaneous Every 2. week Prednisolone 10.2013 - 5,00 mg Peroral Every day
Comorbidity	Vertebral fracture 10.2005 Herpes zoster infection 9.2002 Arm fracture, not wrist 8.2001 Osteopenia by DXA 2001 Cholelithiasis 3.1998 Arterial hypertension 11.1996 Fibromyalgia 7.1990 Lumbago/dorsalgia/sciatica 1980 Migraine - Before rheuma diagnosis
Surgery	Left ankle Arthrodesis 11.2011 Right ankle Arthrodesis 3.2011 Left MTP Arthrodesis 3.2007 Right MTP Arthrodesis 3.2007 Left knee Arthroplasty 10.2003 Left knee Synovectomy 5.2003 Right knee Arthroscopy and Synovectomy 10.2002 Right knee Rearthroplasty 12.2001 Right knee Arthroplasty 4.1998 Right knee Other surgery 8.1996

pain 8, fatigue 12, patient global 9, ESR 2, CRP 5, DAS28 2.1 indicating remission.

Radiographic features: Initial joint radiographs on presentation showed no damage. The most recent radiographs 20-23 years after diagnosis are presented in Fig. 2c. The prominent features are damage in wrists, subluxation of right MCP II, damage of talonavicular and naviculo-cuneiform joints, but minimal erosive changes characteristic of seropositive RA.



Radiographs of the neck in 2007 indicated a sliding atlanto axial subluxation of 7 mm in head bending forward –position. An MRI of the neck showed no active pannus and no erosions in the dens.

### Case 3

**Demographics:** 63 year old female, diagnosed at the age of 28 in 05.1980. Cashier, work disabled since September 1989. Never smoked.

**Initial presentation:** Temporary pains and aches in knees, wrists, and fingers since the age of 15, and increasing several months prior to the diagnosis in 05.1980 when she presented with a polyarthritis as shown in Fig. 3a.

**Comorbidities and Joint surgery:** See Table 3.

**Medications.** Current medications are presented in Table 3. Previous DMARD treatments were (in order): gold i.m., sulphasalazine, auranofin, hydroxychloroquine,

**Table 2** Medical history of Patient 2

Data extracted	15.09.2015
ID	Case 2
Age, Gender	39, Female
Work status	Full-time work
Diagnosis	Rheumatoid Arthritis
Diagnosis criteria	- Symptoms: 3.1992 - Clinical diagnosis of RA: 7.1992
Highest RF (IgM)	Negative (8) 2.2012
Highest (aCCP)	Negative (0) 2.2012
aCarP	Negative 7.2015
HLA-B27	Negative
Drug (now)	Etanercept (Enbrel) 1.2013 - 50,00 mg Subcutaneous Once a week Methotrexate 5.2011 - 15,00 mg Subcutaneous Once a week Prednisolone 4.2004 - 5,00 mg Peroral Every day
Comorbidity	Neutropenia 12.2012 - 12.2012 Viral infection 12.2012 Osteopenia by bone density by DXA 3.2012
Surgery	Neck Arthrodesis 8.2007 Right wrist Tenosynovectomy 10.1995

D-penicillamine, azathioprine, podofyllotoxin (Reumacon), ciclosporin, cyclophosphamide, chlorambucil, leflunomide, and infliximab (Remicade) see Fig. 3b.

Progress: See Fig. 3b. Most recent values for patient reported outcomes and disease activity: HAQ 1.38, pain 0, fatigue 0, patient global 0, ESR 33, CRP 10, DAS28 3.0 indicating low disease activity.

Radiographic features: No radiographic joint damage was seen at initial presentation. The most recent radiographs 32-35 years after diagnosis are presented in Fig. 3c and show prominent damage in the, wrists, ankle/subtalar/upper forefeet areas, as well as status post orthopaedic surgery in many joints.

#### Case 4

Demographics: 60 year old female. Diagnosed at the age of 28 in 12.1982. Waitress, work disabled since 1995, former smoker.

Initial presentation: Symptoms started two years before diagnosis, with synovitis in both knees. Two months prior to diagnosis, symptoms began in other joints with clinical polyarthritis in 12.1982 as presented in Fig. 4a.

Comorbidities and Joint surgery: See Table 4.

Treatment: Current medications are presented in Table 4. Previous DMARD treatments were (in order): Im gold, sulfasalazine, cyclosporine, infliximab, and adalimumab, see Fig. 4b.

Progress: See Fig. 4b. Most recent values for patient reported outcomes and disease activity: HAQ 1.75, pain 59, fatigue 40, patient global 50, ESR 22, CRP 5, DAS28 2.9 indication low disease activity.

Radiographic features: The most recent radiographs of hands, wrists, feet, and ankles, 30-33 years after diagnosis, are presented in Fig. 4c. Destruction of wrists and ankle/subtalar area are prominent, with minimal/no erosions typical for seropositive RA.

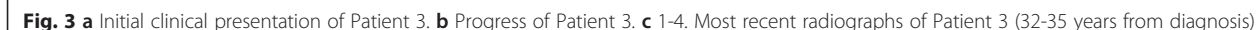
#### Discussion

These cases all share a common feature: that of a severe, destructive disease in seronegative RA with involvement primarily of the wrists, sub-talar and ankle joints, as well as large joints. All these patients were negative with regard to RF, aCCP, and aCarP. Two cases were HLA-B27 positive but despite this, the clinical presentation (signs and symptoms) and radiographs of the sacro-iliac joints did not support a diagnosis of ankylosing spondylitis (AS) or other spondyloarthritides in these individuals.

Seronegative RA has been in focus of only a few cohorts and rarely in detail, to reveal various aspects of outcomes [9]. Again, an exception is from the Heinola group, which reported long-term outcomes of non-specific seronegative oligoarthritis in patients with a 23 year follow-up [16]. Based on patient history, radiographs and clinical status at the follow-up visit, they re-classified the 64 patients and found one case each of RA, systemic lupus erythematosus and ankylosing spondylitis, two cases of post-traumatic arthritis, four cases of osteoarthritis, and six cases of possible reactive arthritis. Of the remaining 49 patients, 15 were HLA-B27 positive and 16 had at least one of the psoriasis-related HLA antigens. Seven patients had minor erosions in their hands or feet joints. One HLA-B27 positive patient had developed bilateral sacroilitis by the evaluation at 23 years. Functional capacity of the patients was well retained. Compared to this Heinola seronegative cohort, our patients present a more severe destructive disease, and to date, remain unclassified.

To our experience, patients with destructive seronegative (RF, aCCP negative) RA - as this disease entity can be referred to - are rare. Among our approximately 3000 RA patients, of whom 30 % are seronegative, only a few seem to present with such degree of destructive disease. However, over the years





The current clinical status of the patients presented in this report indicates considerable functional loss with a HAQ > 1.5 in three of the four patients. Despite this, disease activity appears to be under at least some degree of control with DAS28 values between 2.1 to 3.4. Current treatment in all four patients includes prednisolone, methotrexate and biologic agents (combination of two biologic agents in Case 4).

## Conclusions

Through a detailed description of four destructive seronegative (for RF, aCCP and aCarP) RA cases from disease-onset and up to 35 years from diagnosis, this report could shed more light on the disease presentation, course and outcomes of such patients. We hope to inform the reader of this particular subtype of inflammatory arthritis which can result in

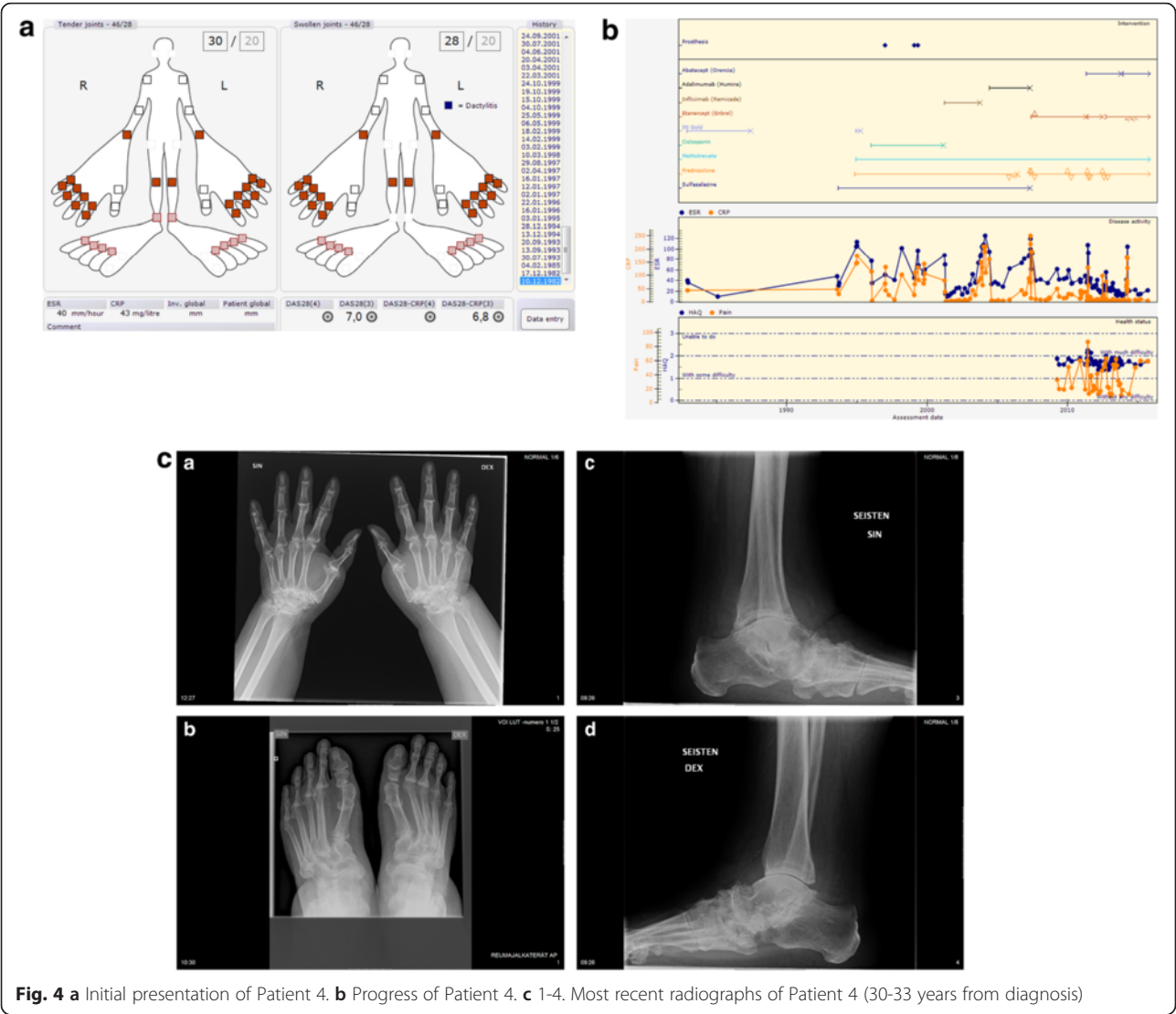
**Table 3** Medical history of Patient 3

Data extracted	14.09.2015
ID	Case 3
Age, Gender	63, Female
Work status	Disabled pensioner since 9.1989
Diagnosis	Rheumatoid Arthritis
Diagnosis criteria	- Symptoms: 6.1979 - Clinical diagnosis of RA: 5.1980
Highest RF (IgM)	Negative (9) 6.2014
Highest (aCCP)	Negative (0) 9.2014
aCarP	Negative 7.2015
HLA-B27	Negative
Drug (now)	Infliximab (Inflectra) 2.2014 - 300,00 mg Intravenous Every 8. week Prednisolone 2.2011 - 2,50 mg Peroral Every day Methotrexate 5.2002 - 10,00 mg Peroral Once a week
Comorbidity	Hyperlipidemia 4.2011 Hypothyroidism 4.2011 Osteoporosis by DXA 11.1997 Arterial hypertension 6.2011
Surgery	Left elbow Prosthesis 2.2011 Right elbow Prosthesis 04.10.2010 Left MCP-1 Arthrodesis 3.2003 Left MCP-4 Prosthesis 3.2003 Left PIP-1 Prosthesis 3.2003 Left PIP-5 Arthrodesis 3.2003 Right DIP-2 Arthrodesis 1.2003 Right MCP-1 Arthrodesis 1.2003 Right MCP-3 Prosthesis 1.2003 Right MCP-4 Prosthesis 1.2003 Right PIP-5 Arthrodesis 1.2003 Right shoulder Prosthesis 12.1997 Left shoulder Prosthesis 9.1997 Right ankle Arthrodesis 9.1996 Right ankle Arthrodesis 1.1996 Left hip Prosthesis 11.1995 Right ankle Arthrodesis 6.1995 Right hip Prosthesis 4.1995

**Table 3** Medical history of Patient 3 (Continued)

Left ankle Arthrodesis 5.1994
Right MCP-3 Prosthesis 11.1993
Right MCP-4 Prosthesis 11.1993
Right MCP-5 Prosthesis 11.1993
Right PIP-1 Arthrodesis 11.1993
Left ankle Arthrodesis 3.1993
Right MTP – Joint resection 1990
Left MTP – Joint resection 1990
Right wrist Tenosynovectomy 2.1981





**Table 4** Medical history of Patient 4

Data extracted	14.09.2015
ID	Case 4
Age, Gender	61, Female
Work status	Pensioner since 1995
Diagnosis	Rheumatoid Arthritis
Diagnosis criteria	- Symptoms: 6.1980 - Clinical diagnosis of RA: 12.1982
Highest RF (IgM)	Negative (8) 4.2009
Highest (aCCP)	Negative (4) 4.2009
aCarP	Negative 7.2015
HLA-B27	Positive
Drug (now)	Abatacept (Orencia) 12.2013 - 125,00 mg Subcutaneous Every week Etanercept (Enbrel) 10.2012 - 50,00 mg Subcutaneous Every 10. day Prednisolone 5.2007 - 5,00 mg Peroral Every day Methotrexate 12.1994 - 20,00 mg Peroral Once a week
Comorbidity	Colon diverticulitis 8.2013 Urinary tract infection 7.2012 Bacterial infection 6.2012 Pulmonary embolism 8.2011 Pulmonary embolism 12.2010 Asthma 11.2008 Hyperlipidemia 1.2008 Arterial hypertension 6.2007 Osteoporosis by DXA measurement 1.1998
Surgery	Right hip Prosthesis 5.1999 Left knee Prosthesis 2.1999 Left hip Prosthesis 1.1997

devastating patient outcomes and therefore needs prompt identification and treatment, similar to seropositive disease. This report justifies the undertaking of further research on the pathogenesis and identification of possible biomarkers for this type of arthropathy, which could be invaluable in firstly understanding disease behavior and course and secondly in treatment stratification.

#### Abbreviations

aCarP, anti-carbamylated protein antibodies; aCCP, anti-cyclic citrullinated peptide antibodies; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease modifying anti rheumatic drug; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IM/i.m, intra muscular; MCP, meta carpo phalangeal; RA, rheumatoid arthritis; RF, rheumatoid factor.

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#### Availability of data and materials

All data concerning the cases are presented in the manuscript or in supplementary material.

#### Authors' contributions

Conception and design (TS), acquisition of data (TS, EN, CS), analysis and interpretation of data, drafting the manuscript and revising it critically for important intellectual content, final approval of the version to be submitted (EN, CS, PH, TR, TS). Each author (EN, CS, PH, TR, TS) has participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

#### Competing interests

The authors declares that they have no competing interests.

#### Consent for publication

Consent to publish the data was obtained from the patients.

#### Ethics approval and consent to participate

The ethics committee of the Hospital District of Helsinki and Uusimaa provided a positive statements for the study (181/13/03/01/2012) and patients signed informed consent.

#### Author details

<sup>1</sup>Rheumatology/Medicine, Jyväskylä Central Hospital, Keskussairaalantie 19, FI-40620 Jyväskylä, Finland. <sup>2</sup>Rheumatology/AIR, Department of Clinical and Experimental Medicine, Linköping University, SE-581 85 Linköping, Sweden. <sup>3</sup>Faculty of Health Sciences, University of Eastern Finland, Jyväskylä Central Hospital, Keskussairaalantie 19, 40620 Jyväskylä, Finland.

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